

CASE REPORT



Deferasirox – a rarer cause of Fanconi syndrome

Iman Khan, Mustafa Muhammad and Janki Patel

Internal Medicine, Greater Baltimore Medical Center, Towson, MD, USA

ABSTRACT

Deferasirox is a recently approved iron chelator and is widely used to treat iron overload in transfusion-dependent patients. Its once-daily dosing and oral route of administration have made it an appealing alternative to deferoxamine. Recent case studies have brought to light its potential to cause damage to the proximal convoluted tubule resulting in Fanconi syndrome (FS). FS is a proximal tubular dysfunction that leads to glycosuria, phosphaturia, aminoaciduria, and normal anion gap metabolic acidosis. Herein, we discuss a case of a young male on chronic blood transfusions requiring deferasirox therapy, who was found to have FS from its use. We discuss the possible mechanism of drug toxicity and the need for regular monitoring of serum electrolytes and urinalysis along with renal function tests to avoid this consequence.

ARTICLE HISTORY

Received 27 May 2019

Accepted 24 July 2019

KEYWORDS

Nephropathy; electrolytes; Fanconi; proximal

1. Introduction

Deferasirox is a recently approved iron chelator and is widely used to treat iron overload in transfusion-dependent patients. Although nephrotoxic side effects of deferasirox are common and include a reversible, mild increase in serum creatinine, its effect on proximal tubule has serious consequences and warrants awareness on the part of prescribers.

2. Case report

A 20-year-old male presented to the emergency department with a one-week history of nausea, vomiting, and watery diarrhea. He had been having loose, watery brown stools without any blood or mucus. He denied any fevers, chills, associated abdominal pain, rectal pain, or tenesmus. He had a past medical history of Diamond–Blackfan anemia for which he was receiving bi-weekly blood transfusions and 24 mg/kg/day deferasirox therapy for secondary iron overload.

Physical exam revealed a dehydrated, cachectic Caucasian male with normal vital signs and a benign abdominal exam. Labs revealed normal white blood cell count, hypokalemia of 2.9 mEq/L, hypophosphatemia of 2.5 mEq/L, low bicarbonate of 18 mEq/L, elevated anion gap of 20 mEq/L, elevated creatinine of 1.6 mEq/L from baseline of 0.8 with estimated glomerular filtration rate of 52 ml/min/1.73 m², and normal glycosylated hemoglobin. Urinalysis revealed a pH of 5, with 3+ proteinuria and 2+ glycosuria. Renal phosphate excretion was indeterminate.

All infectious workup was negative. With the suspicion of Fanconi syndrome (FS) in the setting of

multiple electrolyte abnormalities including glycosuria with euglycemia, further workup was pursued which revealed significant amino acid loss in urine including several essential amino acids, all of which were being excreted in urine at a level 10 times higher than normal.

Since he had no family history of glycogen storage disorders or cystinosis and was on no other medications that could have caused FS (such as valproic acid, cisplatin, tenofovir, and ifosfamide), it was surmised that deferasirox was the likely cause. Multiple myeloma is also a cause of FS and our suspicion was low due to the absence of hypercalcemia. Our suspicion for multiple myeloma was further reduced when we saw improvement in his electrolytes after holding deferasirox while inpatient. His condition improved, and he was successfully discharged home with recommendations to decrease deferasirox. He reported symptomatic improvement and is being followed up for normalization of urinalysis and serum electrolytes.

3. Discussion

Deferasirox is a recently approved iron chelator, widely used to treat iron overload in transfusion-dependent patients. For many years, deferoxamine was the drug of choice for iron chelation therapy. It is given as a subcutaneous injection five to seven times a week, making compliance an issue. Deferasirox, in comparison, is taken orally and dosed once a day, making it a more appealing alternative to deferoxamine [1].

The common side effects of deferasirox therapy include rises in serum creatinine [2]. A mild, transient increase in creatinine of up to two times the

upper limit of normal has been reported by the manufacturers of deferasirox in nearly 38% of the adult patients, of which only 13% patients warranted a dose reduction.

The manufacturers of deferasirox cite the development of FS in 0.1–1% patients [2]. This is generally seen at doses between 20 and 30 mg/kg/day.

Multiple case reports [3,4] have discussed the most likely mechanisms for FS. FS is a generalized proximal tubular dysfunction. As the mechanism of action of deferasirox is its ability to chelate and remove iron, it has been postulated to deplete the iron stores of the mitochondria of the proximal convoluted tubule (PCT) cells [5]. The PCT is a mitochondria-rich part of the nephron and is highly ATP-dependent as it requires energy to facilitate the transport of anions against the electrochemical gradient. When there is mitochondrial damage, PCT cells are not able to synthesize enough ATP to transport electrolytes across the cell membrane [6,7]. This results in their inability to be reabsorbed, and they are lost from the body into the urine.

The major forms of presentation of patients with FS include electrolyte depletion such as phosphaturia, uricosuria, glycosuria, and calciuria. Loss of sodium and chloride ions leads to depletion of extracellular volume, polyuria, consequent dehydration, and polydipsia. Bicarbonaturia leads to the development of acidosis. Loss of essential amino acids in the urine leads to poor developmental state and malnutrition. While a transient increase in creatinine may be acceptable in most patients, FS is a fairly serious adverse effect that may warrant dose reduction or even cessation [8].

While there are no specified criteria to diagnose FS, the constellation of electrolyte abnormalities in the appropriate clinical setting and observing improved electrolyte values with the cessation of inciting factor may be enough to diagnose FS. Renal biopsy is rarely, if ever warranted.

The current monitoring guidelines for deferasirox therapy include monthly renal function tests [2]. This has the potential to miss the development of FS, as providers may be led to believe that the patient may be experiencing a transient rise in creatinine, as is commonly seen with patients on deferasirox and may

not seek further testing. Routine monitoring of serum electrolytes, phosphorus, urinalysis, and urine electrolytes can detect renal tubular dysfunction before symptom onset or complications.

4. Conclusion

Commonly used tests to assess renal function such as estimated glomerular filtration rate and serum creatinine are unable to diagnose FS. Hence, we propose the routine testing of serum electrolytes and urine analysis to facilitate the early diagnosis of FS in patients on chronic deferasirox therapy.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

- [1] Haghpanah S, Zarei T, Zahedi Z, et al. Compliance and satisfaction with deferasirox (Exjade®) compared with deferoxamine in patients with transfusion-dependent beta-thalassemia. *Hematology*. 2013 Nov 25;19(4):187–191.
- [2] Exjade: full prescribing information. Oct 1, 2013. Available from: <https://www.pharma.us.novartis.com/product/pi/pdf/exjade.pdf>.
- [3] Baum M. Renal Fanconi syndrome secondary to deferasirox: where there is smoke there is fire. *J Pediatr Hematol Oncol*. 2010;32(7):525–526.
- [4] Grangé S, Bertrand DM, Guerrot D, et al. Acute renal failure and Fanconi syndrome due to deferasirox. *Nephrol Dialysis Transplantation*. 2010 July;25(7):2376–2378.
- [5] Fucile C, Mattioli F, Marini V, et al. What is known about deferasirox chelation therapy in pediatric HSCT recipients: two case reports of metabolic acidosis. *Ther Clin Risk Manag*. 2018;14:1649–1655.
- [6] Rafat C, Fakhouri F, Ribeil JA, et al. Fanconi syndrome due to deferasirox. *Am J Kidney Dis*. 2009;54:931–934.
- [7] Assmann N, Dettmer K, Simbuerger JM, et al. Reinders renal Fanconi syndrome is caused by a mistargeting-based mitochondriopathy. *Cell Rep*. 2016;15:1423–1429.
- [8] Murphy N, Elramah M, Vats H, et al. A case report of deferasirox-induced kidney injury and Fanconi syndrome. *WMJ*. 2013;112:177–180.